# THE SKIN MICROBIOTA AND ITCH: Is There a Link?

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ABSTRACT

Itch is an unpleasant sensation that emanates primarily from the skin. The chemical mediators that drive neuronal activity originate from a complex interaction between keratinocytes, inflammatory cells, nerve endings, and the skin microbiota, relaying itch signals to the brain. Stress also exacerbates itch via the skin-brain axis. Recently, the microbiota has surfaced as a major player to regulate this axis, notably during stress settings aroused by actual or perceived homeostatic challenge. The routes of communication between the microbiota and brain are slowly being unraveled and involve neurochemicals (i.e., acetylcholine, histamine, catecholamines, and corticotropin) that originate from the microbiota itself. By focusing on itch biology and by referring to the more established field of pain research, this review examines the possible means by which the skin microbiota contributes to itch.

**KEYWORDS:** Itch, skin microbiota, stress, microbiota-skin-brain axis

Bacteria, viruses, fungi, archaea, helminths, and protozoa that inhabit our body are a prospering dynamic community shaping a symbiotic superorganism. Roughly 1,014 microbiota populate the entire body, with their number approximating that of human cells.[1,2] Evidence suggests that microbiota take part in maintaining human health.[3,4]

As a crucial barrier to the exterior world, skin is the body's largest organs.[5] A square centimeter of human skin holds around $10^6$ of microbiota.[6–8] The symbionts defend against illness by regulating the skin barrier and host immune response.[9,10] On the other hand, microbial imbalance (dysbiosis) has been noted to exacerbate skin lesions and delay wound healing.[11,12] Recently, the emerging role of the skin microbiota in itch has received attention.[13] Large-scale changes of the skin microbiota have been noted in itchy skin diseases. *Staphylococcus aureus* (*S. aureus*) participates in atopic dermatitis (AD) flare-up; its colonization correlates with disease severity and itch.[14–16]

In the present review, we offer an integrative perspective on the skin microbiota and itch. The first section describes the interplay of the cutaneous microbiota with the epidermal barrier, the local immune system, and the sensory nerve, proposing the microbiota's peripheral mechanism of itch. The second section concentrates on the concept of microbial endocrinology and addresses the microbiota–skin–brain axis. Moreover, the interaction between the skin microbiota and the amygdala is discussed to explain the microbiota's central mechanism of itch. Overall, this article describes the putative role of the skin microbiota in itch.

## THE PERIPHERAL MECHANISM LINKING THE SKIN MICROBIOTA AND ITCH

Itch arises from the activation of epidermal nerve fibers that belong to a specialized class of itch-provoking neurons ("pruriceptors"). The chemical mediators that drive neuronal activity arise from complex interaction between keratinocytes, inflammatory cells, and nerve endings, coupled with upregulated immune cascades, epidermal barrier dysfunction, and exogenous environmental stimuli (e.g., microbiota, allergens, irritants).[17] Peripheral nerves relay cues from the skin to the dorsal root and trigeminal ganglia and then to the spinal cord and brain where central itch processing takes place (Figure 1).[17]

**Skin barrier.** The skin barrier shields the body from a wide range of external dangers.[18] It consists of the epidermis and several layers below that harbor microbiota.[19–21] The physical skin barrier is the stratum corneum, which comprises dead keratinocytes and proteinaceous crosslinking filaments.[22]

The skin also has a chemical barrier of antimicrobial peptides (AMPs) that are constitutively expressed or induced. AMPs directly block microbial growth or provoke the immune

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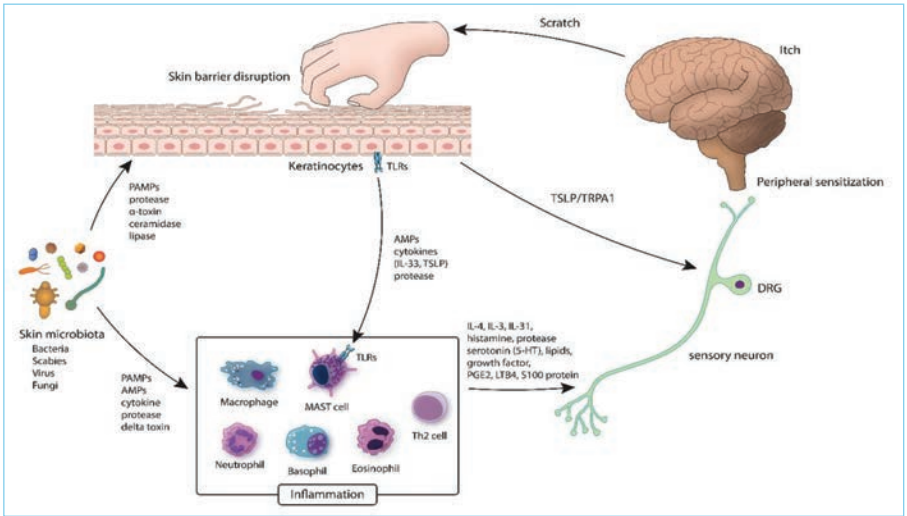


**FIGURE 1.** Inflammatory circuit of the skin microbiota. Various microbiota (bacteria, fungi and viruses) cover the exterior of a healthy skin where the barrier is intact. In the event of dysbiosis, pathogens release proteases, which may disrupt the epidermal barrier. Delta-toxin causes mast cell degranulation, which prompt inflammation and itching. AMP: antimicrobial peptides; DRG: dorsal root ganglia; IL: interleukin; LTB4: leukotriene B4; PAMP: pathogen associated molecular pattern; PGE2: prostaglandin E2; TLR: Toll-like receptor; TRPA1: transient receptor potential antigen 1; TSLP: thymic stromal lymphopoietin. Figure 1. Inflammatory circuit of the skin microbiota. Various microbiota (bacteria, fungi and viruses) cover the exterior of a healthy skin where the barrier is intact. In the event of dysbiosis, pathogens release proteases, which may disrupt the epidermal barrier. Delta-toxin causes mast cell degranulation, which prompt inflammation and itching. AMP: antimicrobial peptides; DRG: dorsal root ganglia; IL: interleukin; LTB4: leukotriene B4; PAMP: pathogen associated molecular pattern; PGE2: prostaglandin E2; TLR: Toll-like receptor; TRPA1: transient receptor potential antigen 1; TSLP: thymic stromal lymphopoietin.

reaction. One example is the liberation of histamine and prostaglandin $D_2$ ($PG\text{-}D_2$)[23] by mast cells in respect to human β-defensins (hβDs) and LL-37, causing pruritus.

The skin microbiota is an integral part of the skin barrier.[18] It protects the host from pathogens by competing for nutrients and space.[19] Some produce antimicrobial compounds that block the growth of competitors.[19] Symbionts also alter the skin barrier via bacterial enzymes, such as proteases, which impact corneocyte desquamation, and lipases, which break down skin surface lipids.[24]

*Staphylococcus epidermidis* (*S. epidermidis*) is the primary bacterium colonizing the human epithelia and is a vital member of the skin resident microbiota.[25] *S. epidermidis* has a flexible interrelation with its host and deposits biofilms (a physical barrier) that are remarkably hard to clear.[26] Symbiont strains of *S. epidermidis* suppress *S. aureus* biofilm formation by producing serine protease (Esp), which also enhances the antimicrobial effect of hβDs.[27] Another typical skin resident is *Cutibacterium acnes* (*C. acnes*), which inhibits the growth of methicillin-resistant *S. aureus* (MRSA).[28] In short, *C. acnes* ferments glycerol, a natural metabolite in human skin, into short-chain fatty acids (SCFAs) that maintain an acidic skin pH.[29] Symbionts flourish at acidic pH, whereas potential pathogens, such as *S. aureus*, thrive at neutral pH.[30,31]

Intrinsic (host) and extrinsic (environmental) factors affect skin barrier function by shaping microbial structure.[32] *S. aureus* colonization is found in up to 90 percent of patients with AD.[33] It produces ceramidase, which breaks down ceramides, an essential component of the skin barrier.[34] *S. aureus* also produces toxins that impede wound healing and bring epithelial barrier disintegration.[35] Scabies mites (*Sarcoptes scabiei*) alter the skin microbiota by breaching the physical barrier.Epidemiologic studies in patients with scabies confirmed secondary bacterial infections by two clinically important pathogens *S. aureus* and *Streptococcus pyogenes*.[36]

Lately, there has been a growing awareness of fungi and their interaction with the skin barrier. When the chemical composition (e.g., sweat, pH) of the host epidermis is disturbed, *Malassezia spp*. acquire pathogenicity and liberate an array of bioactive indoles, lipases, and phospholipases.[37] These molecules further modify the function of the skin barrier.

Epithelial barrier disruption opens the door into a vicious itch–scratch cycle.[38,39] Upon damage or stress, keratinocytes and skin microbiota emit cytokines, AMPs, and proteases that activate immunocytes and nerves.[38,40,41] Protease-activated receptors (PARs), which are cleaved by serine proteases, manifest on different cell types, including sensory neurons and mediate itch.[42–45] β-defensin, an AMP released from epithelial cells, has the ability to stimulate IL-31 production by mast cells.[46] IL-31, initially discovered in 2004, is the first cytokine that is known to facilitate itch by directly operating on sensory neurons (Figure 1).[47]

**The immune system.** Skin is flushed with a wide scope of cells of the innate and adaptive immune system. The skin microbiota keeps immune homeostasis[19] by modulating the expression of diverse innate factors, including AMPs, interleukin 1a (IL-1a),[48] and complement.[49] Symbionts calibrate inflammation.[50,51] *S. epidermidis* suppresses inflammation by inducing IL-10, an anti-inflammatory cytokine, from antigen-presenting cells (APCs).[52] The Toll-like-receptor (TLR)-2-facilitated recognition of lipoteichoic acid (LTA) from *S. epidermidis* inhibits TLR-3-driven inflammatory cytokine production in cultured keratinocytes (Table 1). This also reduces inflammation in wounds, which, when uncontrolled, is damaging to the host.[52] Finally, *S. epidermidis* can finely tune the response of resident T cells and promote selective immunity against skin pathogens.[57]

Alteration in the normal makeup of the skin microbiota can induce inflammation. Moreover, the constitution of the cutaneous microbiota can shift dramatically in the course of inflammation.[14] For example, AD flares have been associated with an expansion of staphylococcal species, which can lead to an overall decrease in microbial diversity.[14] The resulting bacterial and viral infection can cause itch. One possible mechanism of itch from *S.*

**TABLE 1.** Interaction between the skin microbiota and the Toll-like receptors (TLRs).

| BACTERIA | INTERACTIONS WITH TLRS |
|---|---|
| *S. epidermidis* | Adjusts TLR3-dependent inflammation by introducing a TLR2-mediated crosstalk to subdue inflammation.[52]<br>Elicits keratinocytes to display AMPs through a TLR2-dependent mechanism.[50] |
| *S. aureus* | Induction of hBD3 gene expression is TLR2-dependent.[53]<br>Lipoteichoic acid and bacterial lipoproteins act as TLR2/2 or TLR2/6 agonists.[54,55] |
| *P. acnes* | Colonizes sebaceous glands and stimulates keratinocytes to release inflammatory cytokines via TLR2 activation.[56] |

*aureus* infection is mast cell-mediated pruriceptor stimulation. Nunez et al[58] discovered that *S. aureus* releases delta-toxin, an amphipathic peptide that stimulates chemical release from mast cells and mediates skin pathology in AD. Serine protease from *S. aureus* is also involved in type-2 inflammation and itch.[16,59]

Varicella zoster virus (VZV) causes pruritus in chickenpox by mast-cell-derived histamine.[60] Keratinocytes first detect pathogens and initiate an immune response.[61] Keratinocytes identify an array of microbial ligands via Toll-like receptors (TLRs) exhibited on their surface.[62–64] In response to stimulation, keratinocytes produce alarmins or epithelial cell-derived cytokines (i.e., IL-33, thymic stromal lymphopoietin [TSLP]),[65] which potentiate innate and adaptive immunity.[61] TSLP also acts upon a subdivision of TRPA1 sensory neurons to spark itch.[65]

Mast cells are also an essential element of innate immunity. Mast cells recognize pathogens via pathogen-associated molecular pattern (PAMP) receptors (e.g., TLR) on their surface.[66] Once they detect pathogens, inflammatory mediators are released to attract other immune cells.[67,68] Downstream of IL-33 and TSLP, mast cells, neutrophils, basophils, eosinophils, T helper-2 ($T_H2$) cells, and macrophages generate cytokines (IL-4, IL-13, IL-31), histamine, proteases, serotonin (5-HT), lipids, S100 proteins, prostaglandin $E_2$ (PG-$E_2$), leukotriene $B_4$ (LT-$B_4$), and growth factors.[69–71] Recognizing these pro-inflammatory molecules via TRPV1 and TRPA1 channels leads to potential propagation across the afferent itch pathway.[72]

$T_H2$ immunity is dominant in scabies and is complemented by a heavy inflow of IL-31(+) $M_2$ macrophages.[73] Proteases from scabies mite stir epidermal keratinocytes to express TSLP. TSLP activates $T_H2$ cells and induces $M_2$ macrophages to produce IL-31, causing severe itch.[74] The antigens of *S. aureus* have also been reported to induce IL-31 in individuals with AD.[75]

**The sensory nerve.** The skin is one of the human body's first lines of defense against microbial threats. Though the immune system is an essential component of cutaneous immunity, it is evident that the sensory nervous system also plays an important role in host defense. By evoking the sensation of itch, the host can immediately sense danger and rapidly initiate a protective behavioral response.[69]

A network of high- and low-threshold sensory nerves innervates the skin and is frequently exposed to bacterial pathogens (Figure 2). Pruriceptor neurons express cytokine receptors and G protein-coupled receptors that recognize immune mediators.[76] While it is understood that microbial inflammation propagates itch, how the skin microbiota directly triggers sensory nerves is a new area of inquiry. The latest studies suggest that sensory neurons (e.g., immune cells) are able to detect microbiota.[13,69,76,77] Ji et al[78] reported TLR7 on pruriceptors and noted synthetic TLR7 ligands (i.e., imiquimod) causing itch behavior in mice.[78] TLR3 is also displayed by pruriceptors, where Polyl:C, a TLR3 ligand, stimulates neuronal activity and itch.[79] Viral single-stranded RNA and doublestranded RNA are known pathogen-derived ligands for TLR7 and TLR3, respectively, and there is a possibility that these viral ligands cause itch by directly interacting with pruriceptor neurons.[76]

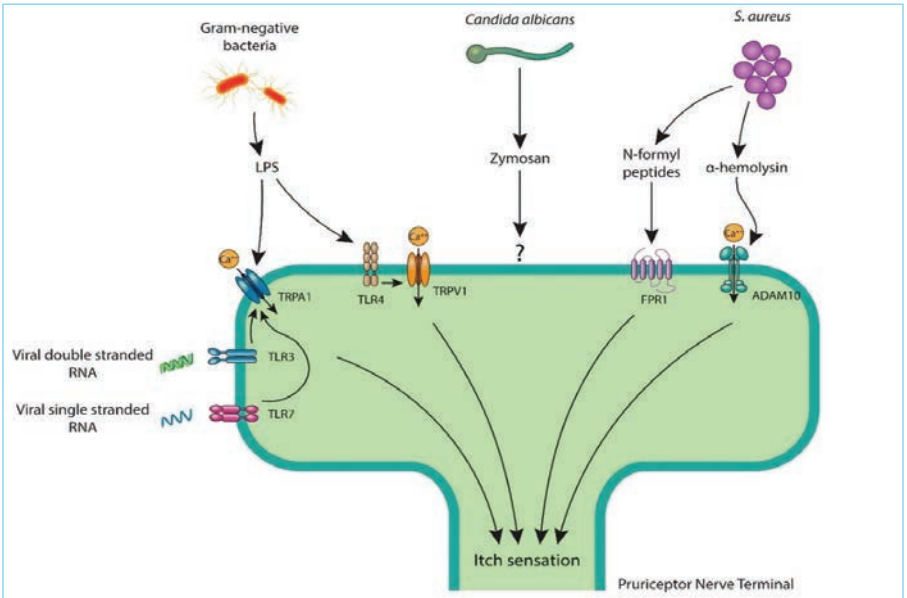


**FIGURE 2.** Pruriceptor neurons recognize skin pathogens and their molecular ligands by various mechanisms to facilitate itch. LPS, a key cell wall component of Gram-negative bacteria attaches to neuronal TLR4 and primes TRPV1 ion channel or opens the TRPA1 ion channel. S. aureus triggers itch with bacterial N-formyl peptides that bind to FPR1 or via α-hemolysin, which couples with ADAM10. C. albicans stimulates pruriceptors with its cell wall component zymosan. Viral double-strand RNA and single-strand RNA bind to TLR3 and TLR7, respectively, which are believed to sensitize the TRPA1 ion channel. ADAM10: a disintegrin and metalloproteinase domain-containing protein 10; FPR1: formyl peptide receptor 1; LPS: lipopolysaccharide; RNA: ribonucleic acid; TLR: Toll-like receptor; TRPA1: transient receptor potential ankyrin 1; TRPV1: transient receptor potential vanilloid 1.

Lipopolysaccharide (LPS), an important component of the Gram-negative bacteria outer membrane binds to TLR4.[80] Although LPS has only been reported with pain,[81] it can also modulate itch since TLR4 promotes histamine-mediated itch.[82] Interestingly, LPS has also been found to stimulate sensory neurons in an TLR4-independent manner, via the activation of TRPA1.[83,84]

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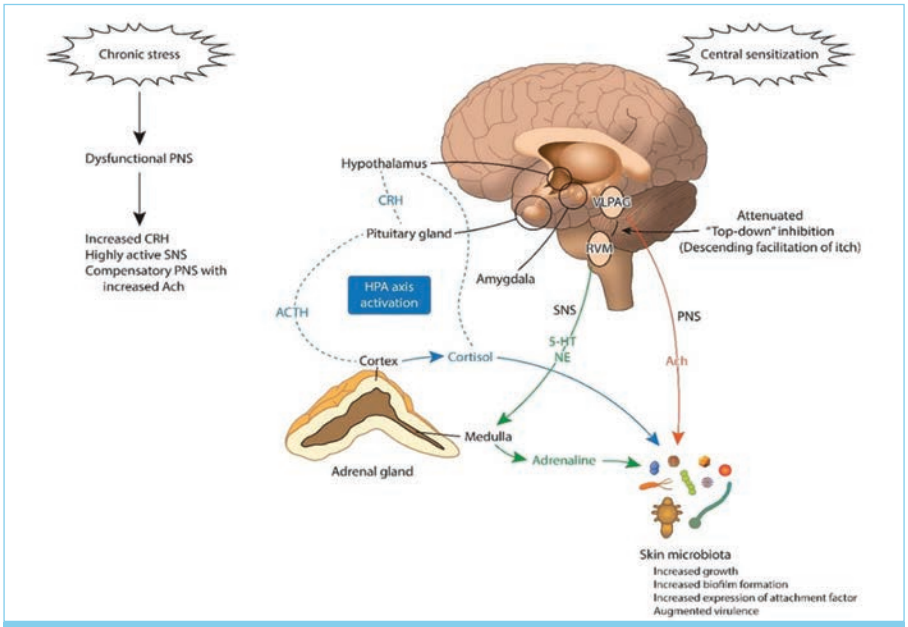


**FIGURE 3.** Brain to microbiota communication under chronic stress. The HPA axis is activated under chronic stress. The final product of the HPA axis, cortisol, directly activates skin microbes. Cortisol activates the amygdala, promoting central sensitization to itch. The amygdala also promotes CRH signaling to the brain stem (PAG), altering the "descending itch modulatory system". Prolonged exposure to cortisol, NE, and ACTH is associated with increased growth and biofilm genesis and augmented virulence of the skin microbiota. Ach: acetylcholine; ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing-hormone; HPA: hypothalamic–pituitary–adrenal axis; 5-HT: serotonin; NE: norepinephrine; PNS: parasympathetic nervous system; RVM: rostral ventromedial medulla; SNS: sympathetic nervous system; VLPAG: ventrolateral periaqueductal grey matter.

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Besides TLR ligands, sensory neurons detect pathogens through various molecular means. Specifically, zymosan from *Candida albicans,*[85] N-formylated peptides and α-hemolysin from *S. aureus*,[86] and *streptolysin S* from *S. pyogens*[87] were shown to mediate pain through direct neuronal stimulation. It remains to be discovered whether pruriceptors similarly detect these pathogens to elicit itch.

Itch is bothersome in patients with cholestatic liver disease.[88] Recently, alteration of the skin microbiota was identified in patients with cirrhosis where specified microbial taxa correlated with itch severity and serum autotaxin (ATX) level.[89] Lysophosphatidic acid (LPA), a powerful neuronal activator, and ATX (ectonucleotide pyrophosphatease/ phosphodiesterase 2), the enzyme that creates LPA, are pruritogens in cholestasis.[90,91] It has been suggested that LPA directly activates TRPV1 on peripheral sensory neurons to mediate itch.[92]

Neuroimmune conversation is bidirectional in itch. Sensory neurons are sensitized by immune cell-made cytokines, such as TNF-α and IL-1β; chemicals, such as histamine; and lipid mediators, such as prostaglandins; which phosphorylate ion channels and lower the bar of action potential firing. Neurons, in turn, secrete neuropeptides (e.g., calcitonin gene-related peptide, substance P) that modulate immune cell function[93,94] and microbial virulence,[95–97] causing itch.[98] Because neurons will respond within milliseconds to danger, the sensory nervous system is likely the body's first detector of pathogen invasion and the prime orchestrator of itch.[76]

## THE CENTRAL MECHANISM LINKING THE SKIN MICROBIOTA AND ITCH

**Microbial endocrinology.** Microbial endocrinology is a combination of two distinct areas of study—microbiology and neurobiology—and is based on the shared presence of neurochemicals in the host and the microbiota.[66] The scope of neurochemicals and the variety of microbiota in which they have been discovered is expansive,[99] including acetylcholine,[100,101] histamine,[102,103] serotonin,[104] catecholamines,[105,106] and agmatine,[107,108] which are essential elements of an animal's nervous system. Others, such as corticotropin,[109] somatostatin,[110] and progesterone,[111] have biological action in mammalian cells. The ability of the microbiota to not only respond to but also create the very same neurochemicals found in mammalian systems indicates that host interplay with its microbiota is more interactive than was prev iously thought. Hence, microbial endocrinology could potentially be applied beyond the study of infectious disease to other conditions, such as neurological disease, through the microbiota–skin–brain axis. Microbiota has multiple transmission pathways to access the brain, including the neural signals carried by the afferent neurons, endocrine messages transmitted by neurochemicals, and the immune response messages transferred by cytokines.[112,113] Supporting cutaneous microbiota improves the skin's barrier functioning and local immune system and assists in its communication with other organ systems, including the brain (microbiota–skin–brain axis).[114]

**Stress.** Stress is a complex, dynamic event

**TABLE 2.** Effects of stress mediators on the skin microbiota.

| BACTERIA | EFFECTS OF STRESS MEDIATORS |
|---|---|
| *Staphylococcus epidermidis* | Glucocorticoids decrease the effects of super antigen activated T cells and inhibit staphylococcal exotoxin-induced T cell proliferation, cytokine secretion.[137]<br>Catecholamines induce biofilm growth.[130] |
| *Propionibacterium acnes* | Cortisol and steroids significantly exacerbate inflammation associated with *P. acnes* via TLR2 stimulation.[138,139] |
| *Pseudomonas aeruginosa* | Norepinephrine increases expression of the attachment factor PA-1 of *P. aeruginosa* and increase biofilm formation.[135,138] |
| *Staphylococcus aureus* | Acetylcholine augments susceptibility to infection by *S. aureus*.[124]<br>Norepinephrine increases *S. aureus*' ability to remove iron from host and therefore facilitates the bacteria to form biofilms.[138,140] |
| *Group A Streptococcus* | Cortisol alters vulnerability to *Group A Streptococcus* pyogenes skin infection.[141]<br>Acetylcholine augments susceptibility to infection by Group A Streptococcus.[124]<br>Catecholamines raise Staphylococcal growth by 5-log orders.[130–132]<br>Catecholamines enhance *Group A Streptococcus* growth likely by increasing iron availability.[138,142] |
| *Candida* | Estrogen enhances Candida infectivity, switching yeast form to an invasive hyphae.[143] |

that alters the body's homeostasis and illicits a response in the host. Stress can aggravate itch,[115–117] which indicates that the brain is engaged in the final common stage of itch processing.[118,119] The stress response by the central nervous system (CNS) can alter the microbiota via the release of neurochemicals.[120,121] Glucocorticoids, essential components of the stress response, repress AMP release/localization in the epidermis, weaken the barrier, and raise host susceptibility to infection.[122–124] Chronic stress is associated with an aberrant parasympathetic tone (Figure 3).[125,126] Cholinergic signaling from physiologic stress[125] can negatively impact the skin barrier and immunity.[127,128] Cathelicidin and β-defensins, AMPs important for innate immunity, are cut down after α7nAChR stimulation,[128,129] leading to bacterial dissemination (Figure 3).[127,128] Skin microbiota, especially the coagulase-negative staphylococci, are sensitive to catecholamines. Norepinephrine (NE), epinephrine, dopamine, and their structurally related inotropes (dobutamine and isoprenaline) raise staphylococcal growth by 5-log orders or more.[130–132] Catecholamines also strengthen bacterial attachment to host tissues and increase bacteria virulence.[130,133,134] Catecholamines stimulate the biofilm formation of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Escherichia coli* (*E. coli*).[124,135] Within a polymirobial biofilm, *P. aeruginosa* enhances USA300 MRSA virulence.[136] Substance P is released in sweat during stress and increases the virulence of Gram-positive skin bacteria, namely *S. aureus* and *S. epidermidis*.[95,96] Thus, the effect of stress on the skin microbiota might be twofold: dampening the host defense to infection and causing changes to the microenvironment that make it more ideal for pathogens.[124] The resultant dysbiosis can exacerbate itch (i.e., "stress aggravated itch") (Table 2).

**The amygdala.** Itch encompasses sensory-discriminative and affective-motivational aspects and undergoes extensive processing in the higher brain centers.[119,125] The amygdala is involved in pain, especially in the emotional-affective aspects of pain perception.[144] The central nucleus of the amygdala (CeA) is commonly called the "nociceptive amygdala"[145] and receives peripheral pain signals via the parabrachial nucleus.[146] The role of amygdala in itch has also been shown in animal studies.[147] A recent study noted that scratching was suppressed after blocking itch-mediating spinal neurons connected to the spinoparabrachial pathway.[148] Additionally, an animal functional MRI (fMRI) study demonstrated amygdala activation during itch stimuli.[149] The findings suggest that itch signals are delivered by both the spinothalamic pathway and the spinoparabrachial-CeA path. Injection of muscimol (γ-aminobutyric acid agonist) to the amygdala appeared to minimize the scratching elicited by the injection of serotonin to the cheek, suggesting a modulatory role of the amygdala in itch processing.[150] Chronic stress brings functional and configurational changes in the amygdala (central sensitization) (Figure 3).[151] This change might influence itch processing in the brain, which might explain why stress can worsen itch in individuals with chronic itch.[152,153] Studies suggest that the amygdala itself is susceptible to microbial influences.[154] Most convincingly, data from germ-free (GF) mice showed hyperactivity in the amygdala transcriptome in the absence of microbiota.[155,156] This hyperactive state is in line with the altered pain sensitivity[157] and stress response in GF mice.[158,159]

Currently, it is not clear how microbial signals navigate through the skin–brain axis to reach the amygdala specifically; however, there are some strong candidate paths, including the blood stream (circulation) and the spinal cord.[112,154,160]

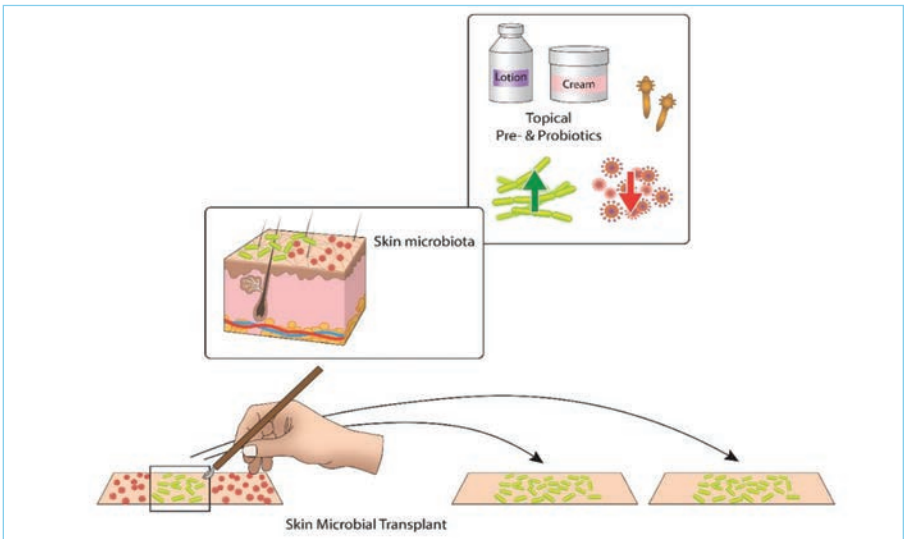


**FIGURE 4.** Two main approaches of controlling the human skin microbiota for the itch control. Topical pre- and probiotics target to increase the number of advantageous bacteria (green) and reduce pathogens (red). Skin microbial transplant is a new approach that transfers beneficial microbiota from healthy skin to itchy and dysbiotic skin.[167]

## CONCLUSION AND FUTURE PERSPECTIVES

Increased recognition and understanding of the presence and functionality of the microbiota has changed what we know about the human body. Cutaneous microbiota appear to have a diverse and far-reaching influence on human physiology by calling upon the host nervous system. Bacteria produce metabolites, toxins, and structural components that are recognized by peripheral and central neurons via matching receptors. Microbiota also appear to indirectly affect neural function by causing endocrine (e.g., keratinocytes) and immune cells to transmit signals (e.g., cytokines, proteases). Itch is a prototypic sensory neural function, and microbiota appear to propel the itch–scratch cycle.

Some descriptive studies have differentiated the microbiota found in itchy skin versus those of healthy skin. While dysbiosis is found in various pathologies, their presence raises a "chicken-or-the-egg" type question in that it remains unclear if dysbiosis leads to disease or the underlying disease results in microbial imbalance. To differentiate cause and effect, a deeper and more mechanistic (functional) understanding of the skin microbiota's role in itch is required. Increased understanding will help us find microbiological markers in itchy conditions and develop more effective therapeutics that utilize host–microbiota relationship. The gut and skin are uniquely related in function, and numerous studies link gut microbiota to skin homeostasis (skin–gut axis or skin–gut–brain axis).[35,161–164] Commonalities have also been found between itch transition in the skin and neural signaling in the lower intestinal tract, which raises the question of whether intestinal microbiota also

play a role in itching.[165,166]

The interplay between the skin microbiota and itch is an emerging area of research with many potential areas of focus for therapeutic development: 1) Whole microbiota transplant, a process that offers microbiota from healthy donors to patients with significant skin dysbiosis, such as AD; 2) Topical probiotics to increase or introduce advantageous microbiota in patients, especially at a critical age for immune and limbic brain wiring; 3) Topical prebiotics to stimulate beneficial skin micrbiota, or biomass or dead extracts of nonpathogenic bacteria to antagonize substance P; and 4) Studies on host–microbiota interplay that analyze microbial metabolites, re-imposing commensal microbial activity by offering signaling molecules (Figure 4).

In future years, we might see topical microbiota modulator cosmetics/transdermal drugs emerge that improve our health as well as our appearance.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the concept and design of the work and approved the submitted version (Conceptualization, H.S.K., and G.Y.; Writing-Original Draft Preparation, Review and Editing, H.S.K., and G.Y.; Funding Acquisition, H.S.K.). All authors have read and agreed to the published version of the manuscript.

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